

## **REMARKS**

Further and favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

### **Claim Status**

Claims 13-16 are pending.

Claims 14-16 are withdrawn from consideration.

Claims 13-16 have been amended to recite Exoenzyme C3 or a Rho kinase inhibitor (ROCK inhibitor) instead of “Rho protein inhibitor.”

Support for such amendments can be found in the specification as filed, for example, page 7, lines 23-26.

New claims 17-20 have been added to the application to further define the ROCK inhibitor.

Support for such claims can be found in the Examples as filed, for example, Experimental Example 2 and Reference Examples 1-3.

No new matter has been added.

### **Information Disclosure Statement**

The Examiner contends that the Information Disclosure Statement filed 1/13/2006 fails to comply with 37 CFR 1.97, 1.98, and MPEP § 609, because several references do not have translations. On the PTO-1449 Form, the Examiner crossed through JP '018, JP '847, JP '581 and JP '513 as not having translations.

MPEP § 609 requires “a concise explanation of the relevance, as it is presently understood by the individual designated in § 1.56(c) most knowledgeable about the content of the information, of each patent, publication, or other information listed that is not in the English language. The concise explanation may be either separate from applicant's specification or incorporated therein.”

MPEP § 609.04(a) sets forth the content requirements for an IDS, and provides more detail regarding the requirement for a “concise explanation of the relevance”. Specifically, MPEP § 609.04(a)(III) states, “If the concise explanation is part of the specification, the IDS

listing should include the page(s) or line(s) numbers where the concise explanation is located in the specification... Where the information listed is not in the English language, but was cited in a search report or other action by a foreign patent office in a counterpart foreign application, the requirement for a concise explanation of relevance can be satisfied by submitting an English language version of the search report or action which indicates the degree of relevance found by the foreign office... This may be an explanation of which portion of the reference is particularly relevant, to which claims it applies, or merely an 'X', 'Y', or 'A' indication on a search report."

In view of the above, Applicants respectfully assert that the requirements of MPEP § 609 (and 37 CFR 1.97 and 1.98) have been satisfied. The Information Disclosure Statement filed January 13, 2006 clearly states that a concise explanation of non-English references is "contained in the specification of the present application at pages 1-8." See item 4(c) on page 3 of the Information Disclosure Statement. Specifically, concise explanations of JP '018, JP '847, and JP '581 appear on pages 2, 3 and 7 of the specification, respectively.

Moreover, JP '513 is cited in the International Search Report (ISR), which was submitted with the Information Disclosure Statement of January 13, 2006. Since the JP '513 reference is designated with a Y indication on page 3 of the ISR, additional explanation is not needed to comply with the requirements of MPEP § 609.

In view of the foregoing, Applicants assert that the Information Disclosure Statement of January 13, 2006 does comply with 37 CFR 1.97, 1.98, and MPEP § 609. Applicants enclose herewith a PTO-1449 Form citing only the references which were not previously considered by the Examiner. Applicants respectfully request the return of an Examiner-initialed copy of the enclosed PTO-1449 Form, thus indicating consideration of the references cited therein.

**Rejection Under 35 U.S.C. § 112, First Paragraph**

Claim 13 is rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. See item 6, pages 3 and 4 of the Office Action. This rejection is respectfully traversed.

Specifically, the Examiner takes the position that the term "Rho protein inhibitor" is not defined in the specification as filed, because it is described by a functional characteristic and not by its structure. Moreover, the Examiner contends that the specification does not adequately

describe the degree of access, binding, or activity to the receptor to allow a person having ordinary skill in the art to ascertain what compounds would fulfill the description.

The current amendment deletes the term “Rho protein inhibitor”, and instead recites Exoenzyme C3 or a Rho kinase inhibitor (ROCK inhibitor).

Compounds 1-4 disclosed in the Examples of the specification are known as ROCK inhibitors. Please see page 7, line 23 to page 8, line 8, Experimental Example 2 and Reference Examples 1-3. Also see Attachment 1.

Exoenzyme C3 (C3 enzyme) is a glycoprotein having a molecular weight of about 24kD, and is known in the art to completely abolish ROCK-I activation. See the Summary of Attachment 2 (Reference 1: Minambres et al., The RhoA/ROCK-I/MLC pathway is involved in the ethanol-induced apoptosis by anoikis in astrocytes, J. of Cell Sci., vol. 119, no. 2, pages 271-282 (2006)).

However, the prior art does not disclose the presence of ROCK I in the trigeminal nerve cell. The Applicants are the first to discover ROCK I and ROCK II in the trigeminal nerve cell. See Experimental Example 3. Moreover, Applicants are the first to verify the corneal nerve neuritogenesis-promoting action of C3 enzyme and ROCK inhibitor. See Experimental Examples 1 and 2.

Further, Applicants point to page 4, lines 9-14 of the Office Action, where the Examiner indicates that the recited compounds are supported by the specification.

Such disclosures in the specification as filed clearly convey to a person having ordinary skill of the art that, at the time the application was filed, the Applicants possessed the invention of amended claim 13. Thus, it is respectfully requested that the rejection be withdrawn.

#### Rejection Under 35 U.S.C. § 103(a)

Claim 13 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Hellberg et al. (WO 03/020281) (hereinafter Hellberg et al.) in view of Lehmann et al. (Inactivation of Rho Signaling Pathway Promotes CNS Axon Regeneration) (hereinafter Lehmann et al.). See item 8 on pages 5 and 6 of the Office Action. This rejection is respectfully traversed.

The Examiner contends that Hellberg et al. teaches the use of compounds that promote neuron regeneration or neurite outgrowth for the treatment of conditions relating to corneal nerve

damage or dry eye. The Examiner concedes that Hellberg et al. does not teach the use of Rho inhibitors. However, the Examiner contends that Lehmann et al. teaches that Rho inhibition fostered regeneration of neurons and yielded extended neurites. Therefore, the Examiner contends that it would have been obvious to a person having ordinary skill in the art to utilize a Rho inhibitor as suggested by Lehmann et al. for treating corneal injury as suggested by Hellberg et al.

Applicants respectfully disagree with the Examiner's position for the following reasons. Hellberg et al. teaches that various compounds promote neuron regeneration or neurite outgrowth. However, as acknowledged by the Examiner, Hellberg et al. does not describe a Rho inhibitor as promoting neuron regeneration or neurite outgrowth. Moreover, Lehmann et al. merely alleges that C3 enzyme shows neuritogenesis-promoting action or regeneration of retinal ganglion cells or the optic nerve, but does not teach the corneal nerve (trigeminal nerve).

The ophthalmic nerve (optic nerve) is very different from the corneal nerve in the origin of nerve, destination of sensory nerves, and function. See Attachment 3, Table 3-3 on page 70 (Reference 2: Fred Delcomyn, Foundations of Neurobiology). Specifically, the function of the ophthalmic nerve is vision, and the destination thereof is the lateral geniculate nucleus (thalamus). In contrast, the function of the corneal nerve is to carry sensory input from the face and control muscles that move the jaw, and the destination thereof is the mesencephalon, pons, and medulla. See Attachment 3 at page 70, Table 3-3 and page 71, Fig. 3-14.

Therefore, it is clear that the optic nerve and the corneal nerve are distinct in function, origin, and destination. Due to such differences, one having ordinary skill in the art would not expect that a substance having neuritogenesis-promoting action or regenerative effect in the optic nerve would have similar effects in the corneal nerve.

Moreover, as described above, the Applicants are the first to discover the presence of ROCK I and ROCK II in the trigeminal nerve cell. It is based on this discovery that the Applicants were able to verify the corneal nerve neuritogenesis-promoting action of C3 enzyme and ROCK inhibitors. Because it was not known that ROCK I and ROCK II are present in corneal nerve cells before the filing of the present application, a person having ordinary skill in the art would not have been motivated to use C3 enzyme, which is a Rho inhibitor only known to

have neuritogenesis promoting action or regenerative effect in the optic nerve, to promote neuritogenesis or regeneration of the corneal nerve, with a reasonable expectation of success.

In view of the foregoing, the rejection is untenable and should be withdrawn.

**Double Patenting Rejection**

Claim 13 is rejected under 35 U.S.C. § 103(a) on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent 7,485,654 (hereinafter US '654). See item 9 on page 6 of the Office Action. [Please note that the Examiner has rejected claim 13 based on claims 19-27 of US '654. However, US '654 contains only claims 1-3. The following arguments are made based on the assumption that the Examiner intended to reject claim 13 based on claims 1-3 of US '654.] This rejection is respectfully traversed.

The Examiner has taken the position that claim 13 of the present invention and the patented claims are not patentably distinct from each other because the patented claims anticipate the broader instant claim.

Claim 13, as amended, recites Exoenzyme C3 or a ROCK inhibitor. Further, the ROCK inhibitor has been limited to one of four compounds having a specific structure (in claim 17). See Attachment 1. The structures of the recited compounds are completely different from the compounds recited in the claims of US '654.

Accordingly, in view of the foregoing reasons, the double patenting rejection has been overcome and should be withdrawn.

### **CONCLUSION**

Therefore, in view of the foregoing amendments and remarks, it is submitted that each of the grounds of rejection set forth by the Examiner has been overcome, and that the application is in condition for allowance. Such allowance is solicited.

If, after reviewing this Amendment, the Examiner feels there are any issues remaining which must be resolved before the application can be passed to issue, the Examiner is respectfully requested to contact the undersigned by telephone in order to resolve such issues.

***The Commissioner is authorized to charge any deficiency or to credit any overpayment associated with this communication to Deposit Account No. 23-0975, with the EXCEPTION of deficiencies in fees for multiple dependent claims in new applications.***

Respectfully submitted,

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2009.07.16 16:48:08 -04'00'

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Attachments: Attachment 1: Chemical Structures of Compounds 1-4 in Examples.

Attachment 2: Minambres et al., The RhoA/ROCK-1/MLC pathway is involved in the ethanol-induced apoptosis by anoikis in astrocytes, J. of Cell Sci., vol. 119, no. 2, pages 271-282 (2006).

Attachment 3: Fred Delcomyn, Foundations of Neurobiology.

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